



Quantum microrheology

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THE UNIVERSITY OF QUEENSLAND

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Final Report

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14. ABSTRACT <p>The project addressed the question: how can quantum optics techniques be translated to improve the performance of biological microscopy? It developed two new approaches to microscopy, improving the precision of both optical tweezers based rheological measurements, and of near-field single molecule sensing. In doing this, the project demonstrated, for the first time, the dramatic improvements that quantum techniques make possible, showing orders of magnitude improvements in both measurement speed and required illumination intensities. 8 peer reviewed papers and 3 conference proceedings were a direct result of the funding.</p>						
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Abstract: The primary objective of this project was to translate techniques from the quantum optics communication – such as those that formed key technology platforms for the successful detection of gravitational waves – into biological microscopy. The project achieved this, developing a quantum light compatible high resolution biological microscope, and a quantum noise limited near-field single molecule sensor. Using the quantum-compatible microscope as an optical tweezer, the project demonstrated ultrafast and ultraprecise measurements of microparticle motion, using this to reach the ballistic motion regime for the first time in a biological optical tweezer and to make nanoscale viscosity measurements orders of magnitude faster than has previously been possible. Using the quantum noise limited biosensor, the motion of single unlabeled molecules was tracked with tens-of-nanometer resolution and optical intensities orders of magnitude lower than has been possible before in a near-field sensor. This opens the door to study the dynamics of the nanoscale machines of life – biological motor molecules – in their native state and without photochemical intrusion.

Introduction:

Quantum optics explores the limits that quantum mechanics imposes on precision measurements; how to reach them, and how to overcome them using quantum correlated (or entangled) photons [1]. Gravitational wave detection is a notable and prominent example [2, 3], where ultralow noise lasers are used in kilometer-scale interferometers to detect the attometer-level distortions in space-time due to catastrophic events in the distant universe. Since the very birth of quantum optics, biological imaging has been identified as a second key area in which techniques developed in the field can be fruitfully applied [4]. Biological imaging, especially at micro- and nanoscale, typically requires high sensitivity and specificity to observe small structures with good contrast, combined with high measurement bandwidths to allow video-rate imaging and to track biological dynamics. Both sensitivity and bandwidth can often be improved by using high optical intensities; as can — in conjunction with nonlinear interactions such as two-photon excitation or Raman scattering [5] — the selectivity. However, the optical intensity cannot be increased indefinitely, since light introduces photodamage to the specimen as well as photochemical intrusion upon biological processes within it [6, 7]. In this scenario, alternative techniques are required to improve optical measurements. This motivates the central question of this project: how can the information extracted about a specimen be maximized per photon that is used to probe it?

This question has motivated many developments over several decades in the quantum and precision measurement communities, as best exemplified by the advances in precision engineering and fundamental science which enabled the successful detection of gravitational

waves reported this year [2, 8, 9]. In 2013–2014, our laboratory began to translate these ideas into biological applications, showing that quantum correlated photons allow viscoelasticity measurements within a cell with both improved speed over conventional approaches [10] and nanoscale resolution [11]. This AFOSR/AOARD project has continued this development focusing on enhancing the performance of optical tweezers and near-field biosensors, and applications in microrheology, the study of energy storage and dissipation in soft matter systems.

The aims of the project included to:

- Develop a quantum-light compatible high-resolution microscope.
- Reach the quantum noise limit for a near-field single-molecule biosensor.
- Detect and track an unlabeled single molecule with nanoscale precision and optical intensity beneath known biological damage thresholds.
- Demonstrate ultrafast and ultrasensitive quantum noise limited microrheology.



Figure 1: Photographs of AFOSR students and postdoc working on their experiments. People from left to right: Catxere Casacio, Muhammad Waleed, Lars Madsen (postdoc) and Nicolas Mauranyapin. Experiments: (left) ultrahigh bandwidth optical tweezer, (middle) source for quantum microscopy experiments, (right) near-field quantum-limited biosensor.

Experiment: Description of the experiment(s)/theory and equipment or analyses.

The research project had two distinct but closely aligned themes: ultrahigh bandwidth optical tweezers for nanoscale rheology, and quantum-limited near-field probing of unlabeled single molecule dynamics. We discuss the experiments performed on each separately in what follows, beginning with a brief overview of the quantum optics approach to precision measurement.

Quantum optics techniques for precision measurement

The primary focus of precision measurement efforts in the quantum optics community has been to develop techniques that maximize the information extracted from a given specimen per photon used to interrogate it. Generally, this is achieved by separating the measurement process into five parts as shown in Fig. 2. The laser source is engineered to minimize the presence of noise at relevant frequencies, with quantum correlated photons allowing noise levels even beneath the shot noise present due to the quantization of light. Optical systems such as interferometers,

optical cavities and adaptive optics are used to prepare the laser field so as to optimize its interaction with the specimen. After interaction with the specimen further optical systems are used to filter the output field to reduce background noise and match the signal encoded on the optical field to photodetectors that are designed with ultrahigh efficiency and electronic noise far below the optical shot noise floor. Gravitational wave interferometry is the canonical example of such as process, with major efforts undertaken over the course of fifty years to achieve measurement precision at the level of attometers-per-root-hertz on a four kilometer arm length, equivalent to a thousandth of the diameter of a proton. This project applied this quantum optics philosophy for precision measurement to the biosciences applications discussed below.



Figure 2: Elements of an optical measurement

Ultrahigh bandwidth optical tweezers

Optical tweezers are an important tool to study and control processes occurring at nanoscale within living biological systems. Among other applications, they allow the manipulation of viruses and bacteria [15], measurements of the unfolding of single RNA molecules [16], DNA sequencing [17] and characterization of the step-like motion of motor molecules [16, 18]. The ability to measure particle mobility in real-time within living cells [19] has revealed information about motor proteins, chemical gradients, protein polymerization [20], the viscoelasticity of the cytoplasm [21] and viscoelastic changes during dynamic cellular processes [22], among many other insights.

Many applications of optical tweezers rely on the ability to track the position of nanoparticles trapped within the laser field with high precision. The measurement precision dictates the speed at which information can be extracted from the specimen, constraining both the rate of imaging and the speed of biological dynamics that can be probed. In Ref. [23], we showed that the fundamental limit to precision imposed by quantum mechanics is approximately two orders of magnitude superior to what is achieved in the best existing optical tweezers; with the use of quantum correlated photons allowing even this limit to be surpassed. In efforts to approach the quantum precision limit, in this AFOSR/AOARD project we have developed an ultrahigh efficiency high resolution microscope and a quantum noise limited detection system which are both compatible with quantum correlated photons (see Fig. 1). This has allowed us to perform the fastest measurements ever made in a biological optical tweezers, and apply these measurements to extract biophysical information with precision and speed faster than has previously been possible, as discussed further in the results section.

Quantum-limited near-field biosensor

Evanescent optical biosensors that operate label-free and can resolve single molecules have applications ranging from clinical diagnostics [26, 29], to environmental monitoring [27, 28] and

the detection and manipulation of viruses [30], proteins and antibodies [31, 32, 33]. They, further offer the prospect to provide new insights into motor molecule dynamics and biophysically important conformational changes as they occur in the natural state, unmodified by the presence of fluorescent markers or nanoparticle labels [31]. Recently, the reach of evanescent techniques has been extended to single proteins with Stokes radii of a few nanometers [32, 29] by concentrating the optical field using resonant structures such as optical microcavities [31, 30, 27, 34] and plasmonic resonators [32, 29, 33]. These advances illustrate a near-universal feature of precision optical biosensors — that, to detect smaller molecules or improve spatiotemporal resolution, increased light intensities are employed. This increases the photodamage experienced by the specimen, which can have broad consequences on viability [35], function [36], structure [37] and growth [38]. It is, therefore, desirable to develop alternative biosensing approaches that improve sensitivity without exposing the specimen to higher optical intensities.

Within this AFOSR/AOARD research project, we developed a new optical nanofiber-based approach to evanescent detection and tracking of unlabeled biomolecules [39, 13, 14] that utilizes a combination of heterodyne interferometry and dark field illumination [40, 41] (see Fig. 6 (top)). This greatly suppresses technical noise due to background scatter, vibrations and laser fluctuations that has limited previous experiments [42, 43], allowing operation at the quantum noise limit to sensitivity introduced by the quantization of light. The technique opens the door to detect the presence of unlabeled biomolecules, and to track their motion, with precision superior to all previous optical techniques. As discussed in the result section, we have done this, setting the stage for future experiments studying motor molecule dynamics in their native state.

Sub-nanometer resolution imaging of optical nanofibers. A key technology that we developed for our near-field biosensing experiments is a technique to non-destructively characterize the profile of optical nanofibers with sub-nanometer precision [13] (see Fig. 3). This technique is the only existing technique capable of immediate non-destructive characterization has higher resolution than is possible with other techniques including scanning electron microscopy, and provides information required to both predict and optimize the performance of our biosensor.

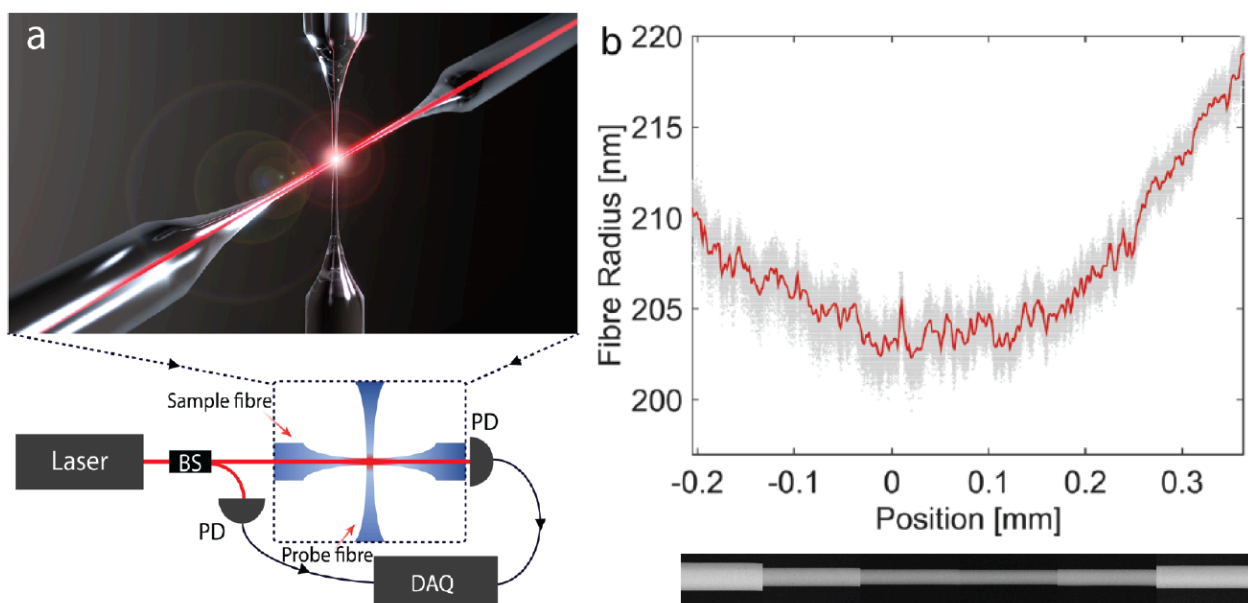


Figure 3: Optical technique to characterize optical nanofibers with sub-nanometer precision [13]. (a) Experimental setup. (b) Top: Experimentally characterized nanofiber profile. Bottom:

Scanning electron micrograph images of the nanofiber, confirming accuracy of the optical technique.

Results and Discussion:

As introduced above, our most significant technical accomplishments from this project include the development of a quantum-light compatible high-resolution microscope, the use of structured light to greatly enhance the interaction between light and particles trapped in an optical tweezer [12] (see Fig. 4), and reaching the quantum limit to precision in a near-field single-molecule biosensor [13, 14]. These developments provide a platform for new applications of quantum measurement in the biological sciences, from improved imaging of structures in cells to the observation and imaging of single motor molecule dynamics and neuronal activity. They, further, offer the possibility to study the effect of optical and radio frequency radiation on the function of biological matter in its natural state, and at the single molecule level. This could, for instance, provide a better understanding of the effects of bio-stimulation in cellular biology; and ultimately the impact of radiation and other sub-cellular stimulants on human performance. Further details of these accomplishments, and applications of them, are given in what follows.

Ultrahigh bandwidth optical tweezers

The quantum-light compatible optical tweezer developed in this project enables optical particle tracking with measurement bandwidth more than two orders-of-magnitude superior to that achieved in previous biological optical tweezers [24]. This has allowed us to reach, for the first time, the ballistic motion regime of particle tracking in a biological optical tweezer. In this regime, the measurement is sufficiently fast to resolve the coherent ballistic particle trajectories, in-between the usual Brownian random walk characteristic of thermal diffusion. This means that a fundamentally new regime of sensing can be reached – taking advantage of coherent particle dynamics, rather than just random diffusion. We have demonstrated two sensing applications within this regime. Firstly, showing that it allows nanoscale measurements of viscosity three orders of magnitude faster, and with higher precision, than any previous optical tweezers-based technique [58]. Secondly, showing that it allows the particle velocity distribution to be characterized in a biological fluid. This distribution is widely important for biochemical modelling, such as of reaction rates and nutrient diffusion. However, to-date, it has not been possible to directly measure it.

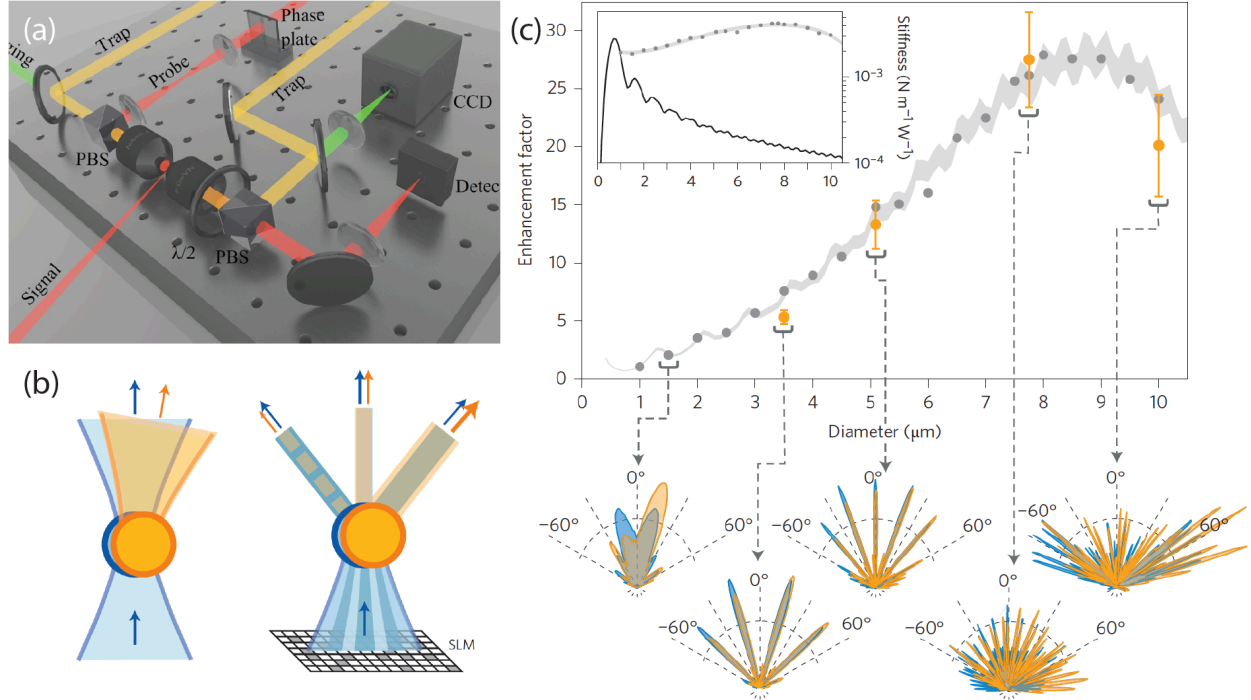


Figure 4: Quantum enhanced optical tweezers. (a) Schematic of apparatus developed in Ref. [10] integrating quantum correlated photons with optical tweezers, and enabling performance beyond the quantum noise limit. (b) Concept of technique developed in Ref. [12] to enhanced the interaction strength between trapped particles and incident photons. (c) Enhancements in trap stiffness as large 27 times were achieved for large particles, along with more than two-orders-of-magnitude improvement in signal-to-noise.

We have, further, shown that the light-particle interaction can be enhanced by more than a factor of ten for large particles by structuring the phase profile of the incident optical field to engineer the scattering from the particle [12] (see Fig. 4). In collaboration with colleagues at the Denmark Technical University we have demonstrated that quantum correlated light can be used to improve the tracking and control of motion at sub-nanoscale [25] (see Fig. 5).

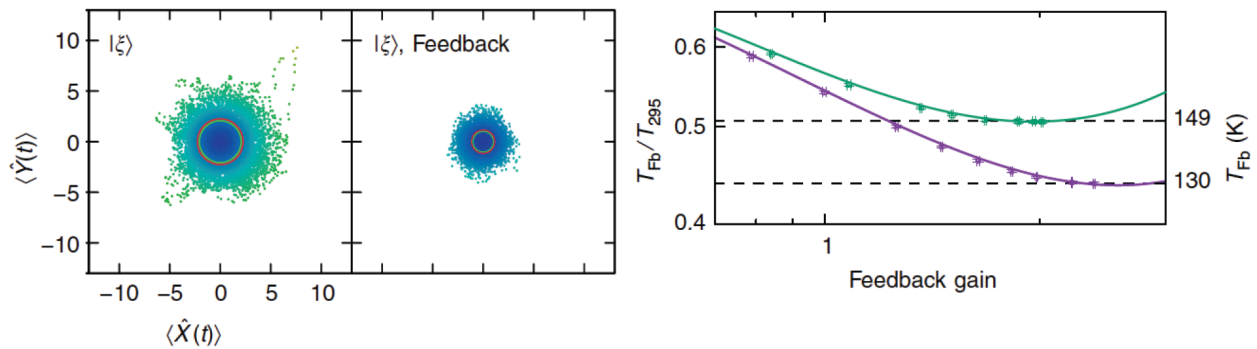


Figure 5: Demonstration of quantum-enhanced tracking and control of mechanical motion using quantum correlated light [25]. Here, the motional degree of freedom was a mechanical eigenmode of a microtoroidal optical cavity, though the technique can be applied equally into the tracking of motion of biological specimens.

Quantum-limited near-field biosensor

The increased information that is extracted per scattered photon in our dark-field quantum noise limited biosensor enables state-of-the-art sensitivity to be achieved with optical intensities four orders of magnitude lower than has been possible previously [29, 32]. This dramatic improvement in performance opens the door to explore the dynamics of nanoscale biomolecules in their native state and without photo-induced changes to their dynamics. This capability is demonstrated in Fig. 6 (bottom), where the dynamics of two biomolecules are tracked with ~50 nm spatial resolution and millisecond temporal resolution. Here, the smaller biomolecule (Bovine Serum Albumin) has a radius of 3.5 nm and molecular mass of around 67 kDa. Importantly, the ability to operate at light intensities below known biological damage thresholds [14] will allow the effects of optical and radio frequency radiation to be studied at the single-molecule level as a function of the intensity of the radiation, without interference from the measurement apparatus. This has the potential to provide qualitatively new insights into the effect of radiation on sub-cellular biophysical processes and ultimately on human performance. The new technique we have developed, combined with our collaboration with Drs. Beier and Bixler at the ARFL and access to their expertise in both in the application of radio and optical frequency radiation to biological systems and in the interpretation of experimental results, place us in a unique position to do research in this area.

One interesting aspect of our nanofibre sensing experiments is that it appears that the presence of an electric double layer—where positive charges are attracted to the negatively charged surface of the particle—significantly enhances the scattered power from particles in the sensing region, and therefore improves the performance of the sensor [14]. This is consistent with recent observations of electric-double layer enhanced trapping of sub-200 nm micelles in optical tweezers [44] which also relies on dipole scattering, and may explain controversial existing results in the evanescent biosensing literature [45].

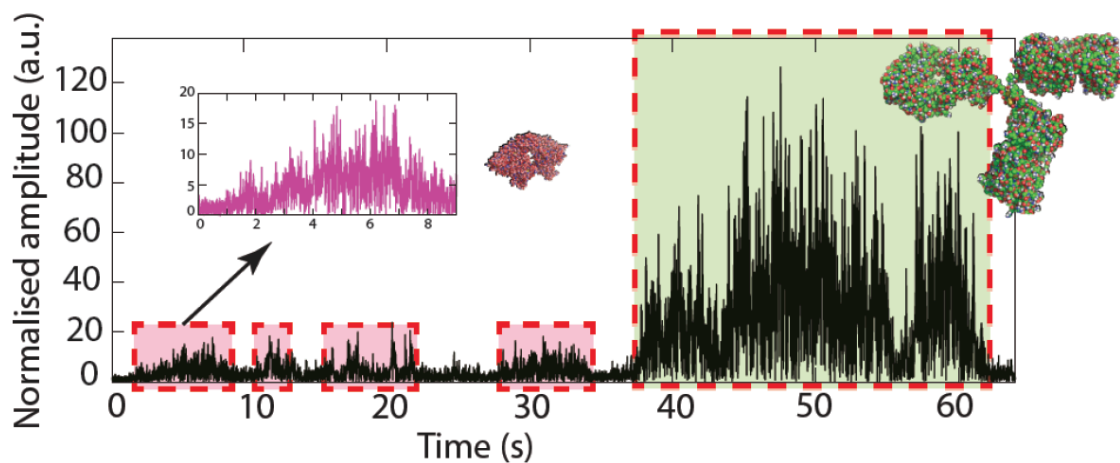
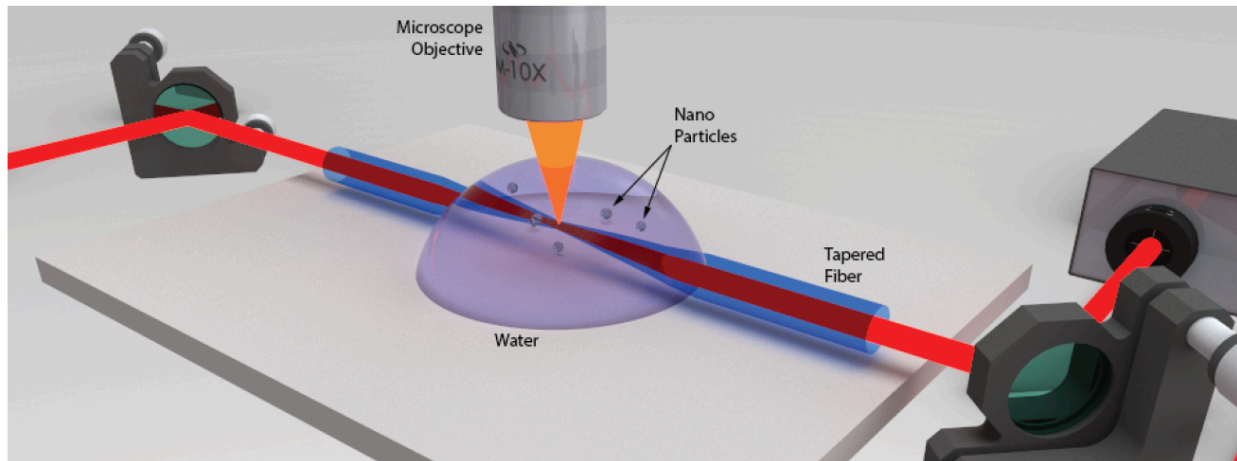


Figure 6: Quantum-limited near-field biosensor. (top) Schematic of apparatus. (bottom) Tracking of biomolecule dynamics with millisecond resolution. Purple shading: dynamics of Bovine Serum Albumin (purple). Green shading: anti-E. Coli antibody. Here, the log of the vertical axis is proportional to the distance the molecule is away from the nanofibre surface, with calibrated resolution for each molecule in the range of 50 nanometers.

References:

- [1] M. A. Taylor and W. P. Bowen, *Physics Reports* 615 , 1-59 (2016).
- [2] B P Abbott et al. , *Rep. Prog. Phys.* 72 076901 (2009).
- [3] W. P. Bowen and G. J. Milburn, *Quantum optomechanics* CRC Press (2016).
- [4] R. E. Slusher, *Quantum Optics in the '80s* , *Optics and Photonics News*, December 1990.
- [5] See e.g. E. E. Hoover and J. A. Squier, *Nature Photonics* 7 , 93-101 (2013).
- [6] E. J. Peterman, F. Gittes, and C. F. Schmidt, *Biophys. J.* 84 13081316 (2003).
- [7] K. C. Neuman, E. H. Chadd, G. F. Liou, K. Bergman, and S. M. Block, *Biophys. J.* 77 2856-2863 (1999).
- [8] B. P. Abbott et al. , *Phys. Rev. Lett.* 116 241103 (2016)
- [9] J. S. Bennett and W. P. Bowen, *Nature Physics News & Views* 12 , June 2016.
- [10] M. A. Taylor, J. Janousek, V. Daria, J. Knittel, B. Hage, H.-A. Bachor and W. P. Bowen, *Nature Photonics* 7 229-233 (2013).
- [11] M. A. Taylor, J. Janousek, V. Daria, J. Knittel, B. Hage, H.-A. Bachor and W. P. Bowen,

Phys. Rev. X 4 , 011017 (2014).

[12] M. A. Taylor, M. Waleed, A. B. Stilgoe, H. Rubinsztein-Dunlop and W. P. Bowen, Nature Photonics, 9 669-674 (2015).

[13] L. S. Madsen, C. Baker, H. Rubinsztein-Dunlop and W. P. Bowen, Nano Letters 16 7333-7337 (2016).

[14] N. P. Mauranyapin, M. A. Taylor, L. S. Madsen, M. Waleed and W. P. Bowen, Evanescent single-molecule biosensing with quantum limited precision , Nature Photonics 17 477-482 (2017).

[15] A. Ashkin, A. and J. Dziedzic, Science 235 1517-1520 (1987).

[16] K. C. Neuman and A. Nagy, Nature Methods 5 491-505 (2008)

[17] W. J. Greenleaf and S. M. Block, Science 5 801 (2006).

[18] J. T. Finer, R. M. Simmons, and J. A. Spudich, Nature 313 113-119 (1994).

[19] S. Yamada, D. Wirtz, and S. C. Kuo, Biophys. J. 368 1736-1747 (2000).

[20] E. N. Senning and A. H. Marcus, Proc. Natl Acad. Sci. 78 721-725 (2010).

[21] I. M. Tolic-Nrrelykke, E.-L. Munteanu, G. Thon, L. Oddershede, and K Berg-Srensen, Phys. Rev. Lett. 93 078102 (2004).

[22] C. Selhuber-Unkel, P. Yde, K. Berg-Srensen, and L. B. Oddershede, Phys. Biol. 6 025015 (2009).

[23] M. A. Taylor, J. Knittel and W. P. Bowen, New Journal of Physics, 15 023018 (2013).

[24] G.H. Koenderink, M. Atakhorrami, F.C. MacKintosh, and C.F. Schmidt, Phys. Rev. Lett. 96 138307 (2006).

[25] C. Schaefermeier, H. Kerdoncuff, U. B. Hoff, H. Fu, A. Huck, J. Bilek, G.I. Harris, W. P. Bowen, T. Gehring and U. L. Andersen, Nature Communications 7 , 13628 (2016).

[26] M. Piliarik and V. Sandoghdar, Nature Communications 5 4495 (2014).

[27] J. Zhu, S. K. Ozdemir, Y.-F. Xiao, L. Li, L. He, D.-R. Chen and L. Yang, Nature Photonics 4 46-49 (2010).

[28] B.-B. Li, W. R. Clements, X.-C. Yu, K. Shi, Q. Gong and Y.-F. Xiao, PNAS 111 14657-14662 (2014).

[29] V. R. Dantham, S. Holler, C. Barbre, D. Keng, V. Kolchenko and S. Arnold, Nano Letters 13 3347-3351 (2013).

[30] F. Vollmer, S. Arnold and D. Keng, PNAS 105 20701-20704 (2008).

[31] M. D. Baaske, M. R. Foreman and F. Vollmer, Nature Nanotechnology 9 933-939 (2014).

[32] Y. Pang and R. Gordon, Nano Letters 12 402-406 (2012).

[33] P. Zijlstra, P. M.R. Paulo and M. Orrit, Nature Nanotechnology 7 379-382 (2012).

[34] J. D. Swaim, J. Knittel and W. P. Bowen, Applied Physics Letters 102 183106 (2013).

[35] U. Mirsaidov, W. Timp, K. Timp, M. Mir, P. Matsudaira and G. Timp, Phys. Rev. E. 78 021910 (2008).

[36] Y. Sowa, A. D. Rose, M. C. Leake, T. Yakushi, M. Homma, A. Ishijima and R. M. Berry, Nature 437 916-919 (2005).

[37] M. P. Landry, P. M. McCall, Z. Qi and Y. R. Chemla, Biophys. J. 97 2128-2136 (2009).

[38] S. Wäldchen, J. Lehmann, T. Klein, S. van de Linde and M. Sauer, Scientific Reports 5 15348 (2015).

[39] J. D. Swaim, J. Knittel and W. P. Bowen, Applied Physics Letters 103 203111 (2013).

[40] M. A. Taylor, J. Knittel and W. P. Bowen, Optics Express 21 , 8018 (2013).

[41] Michael A. Taylor and Warwick P. Bowen, Applied Optics 52 5718-5723 (2013).

[42] J. Knittel, J. D. Swaim, D. L. McAuslan, G. A. Brawley, W. P. Bowen, Scientific Reports 3 2974 (2013).

[43] T. Lu, H. Lee, T. Chen, S. Herchak, J. Kim, S. E. Fraser, R. C. Flagan, K. Vahala, PNAS

108 5976-5979 (2011).

[44] S. Park et al. , Soft Matter 10 8406 (2014).

[45] A. M. Armani, R. P. Kulkarni, S. E. Fraser, R. C. Flagan, K. J. Vahala, Science 317 783-787 (2007).

[46] C. H. Camp and M. T. Cicerone, Nature Photonics 9 2965-305 (2015).

[47] See e.g. C. W. Freudiger et al. , Science 322 1857-1861 (2008).

[48] B. G. Saar et al. , Science 330 1368-1370 (2010).

[49] W. Rock, M. Bonn and S. H. S. Parekh, Optics Express 21 15113-15120 (2013).

[50] F.-K. Lu et al. , Cancer Research 76 2451-3462 (2016).

[51] F.-K. Lu et al. , Proc. Nat. Acad. Sci. 112 11624-11629 (2015).

[52] L. Wei et al. Nature Methods 11 410-412 (2014).

[53] P. V. Alfonso et al. Dev. Cell 22 1079-1091 (2012).

[54] R. Arora, G. I. Petrov, V. V. Yakovlev and M. O. Scully, Proc. Nat. Acad. Sci. 109 1151-1153 (2012).

[55] B. Liu et al. Applied Physics Letters 106 173704 (2015).

[56] D. Zhang et al. Label-free imaging of single neuron activities by stimulated Raman scattering , CLEO: Applications and Technology, 10-15 May 2015, page AM3J.4, ISBN: 978-1-55752-968-8.

[57] C. W. Freudiger et al., Nature Photonics 8 153-159 (2014).

[58] M. Waleed et al., in preparation (2018).

List of Publications and Significant Collaborations that resulted from your AOARD supported project:

a) papers published in peer-reviewed journals,

(i) Evanescent single-molecule biosensing with quantum-limited precision. N. P. Mauranyapin, L. S. Madsen, M. A. Taylor, M. Waleed and W. P. Bowen, Nature Photonics 11, 477-481 (2017). Impact Factor: 31.17.

(ii) Quantum enhanced feedback cooling of a mechanical oscillator using nonclassical light. C. Schafermeier, H. Kerdoncuff, U. B. Hoff, H. Fu, A. Huck, J. Bilek, G. I. Harris, W. P. Bowen, T. Gehring and U.L. Andersen, Nature Communications 7, 13628 (2016). Impact Factor: 11.33.

(iii) Quantum metrology and its application in biology. M. A. Taylor and W. P. Bowen, Physics Reports 615, 1-59 (2016). Impact Factor: 20.03.

(iv) Nondestructive Profilometry of Optical Nanofibers. L.S. Madsen, C. Baker, H. Rubinsztein-Dunlop, and W.P. Bowen, Nano Letters 16 7333-7337 (2016). Impact Factor: 13.78.

(v) Quantum Optomechanics, Warwick P. Bowen and Gerard J. Milburn, CRC Press, ISBN 9781482259155 (2016). First textbook in the field of quantum optomechanics.

(vi) Factors affecting the $f \times Q$ product of 3C-SiC microstrings: What is the upper limit for sensitivity? A. R. Kermany, J. S. Bennett, G. A. Brawley and W. P. Bowen, F. Iacopi, J.

Appl. Phys. 119, 055304 (2016). Featured on front cover. Impact Factor: 2.10.

(vii) Potential of epitaxial silicon carbide microbeam resonators for chemical sensing. A. R. Kermany, J. S. Bennett, V. M. Valenzuela, W. P. Bowen and F. Iacopi, Phys. Status Solidi A. DOI 10.1002/pssa.201600437 (2016). Impact Factor: 1.65.

(viii) Evanescent single-molecule biosensing with quantum limited precision. N. P. Mauranyapin, L. S. Madsen, M. A. Taylor, M. Waleed, W. P. Bowen. Nature Photonics **17** 477-482 (2017). Impact Factor: 31.17.

b) papers published in non-peer-reviewed journals or in conference proceedings,

(i) Sensing past the quantum limit. C.G. Baker and W.P. Bowen, Nature, News and Views 547 164 (2017). Impact Factor: 40.137.

(ii) Quantum measurement: Coping with pressure. J.S. Bennett and W.P. Bowen, Nature Physics, News and Views 10 (2016). Impact Factor: 18.79.

(iii) Viewpoint: Quantum Squeezing of Micromechanical Motion. Warwick P. Bowen, Physics 8, 119 (2015).

c) conference presentations,

(i) Quantum microscopy: probing nanoscale biological machinery in its native state, W. P. Bowen, Plenary, New Frontiers in Quantum Imaging Symposium, Glasgow, June 2017.

(ii) Quantum microscopy: probing nanoscale biological machinery in its native state, W. P. Bowen, Plenary, Australian Institute of Physics Summer Meet, December 2017.

(iii) Single biomolecule detection with quantum-limited precision: towards the observation of nanoscale biological machinery in its native state, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, Invited, Smart Sensing, Rome, March 2017.

(iv) Quantum-limited single molecule biosensing, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, Invited, Heraeus Seminar on Quantum-limited Metrology and Sensing, Bad Honnef, Feb 2017.

(v) Quantum-limited single molecule biosensing: probing nanoscale biological machinery in its native state, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, Invited, International Symposium on the Physics of Quantum Electronics, Snowbird, Utah, 2017.

(vi) Single molecule biosensing at the quantum limit, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, Invited, Foundations of Quantum and Mesoscopic Thermodynamics, Prague, June 2017.

(vii) Quantum-limited evanescent single molecule sensing, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, APS March Meeting, New Orleans, March 2017.

(viii) Quantum-limited single molecule sensing: probing nanoscale biological machinery in its native state, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, Invited, Central European Workshop on Quantum Optics, June 2017.

(ix) Quantum enhanced nonlinear microscopy, C. Casacio, L. Madsen and W. P. Bowen, Australian Institute of Physics Congress, Brisbane, Australia 2016.

(x) Quantum sensors and metrology, W. P. Bowen, invited overview talk, Australian Centre for Engineered Quantum Systems Annual Workshop, Brisbane, Australia, December 2016.

(xi) Evanescent single-molecule biosensing with quantum limited precision, N. P. Mauranyapin, M. A. Taylor, L. Madsen, M. Waleed and W. P. Bowen, Australian Institute of Physics Congress, Brisbane, Australia 2016.

(xii) Quantum constraints to biological measurement, and how to overcome them, Warwick Bowen, AFOSR Biophysics Review Meeting, Dayton, United States, Nov. 2016

(xiii) Quantum techniques for biological sensing and microscopy, Warwick Bowen, AFOSR Biophysics Review Meeting, San Antonio, United States, Nov. 2015

(xiv) Quantum measurement and control in biology, Warwick Bowen, AFOSR Visit to the University of Queensland, October 2015

(xv) Quantum enabled sensors and metrology, Warwick Bowen, invited program overview talk, Australian Centre for Engineered Quantum Systems Annual Workshop, December 2015

(xvi) Non-destructive detection and trapping of nanoscale biomolecules, N. Mauranyapin, L. Madsen, M. Waleed, C. Catxere and W. Bowen, invited talk, Enabling Technologies Technical Exchange Meeting, AFOSR/ANFF, Sydney, Australia, May 2016

(xvii) Quantum constraints to biological measurement and how to overcome them, Warwick Bowen, invited talk, Gordon Research Conference on Lasers in Medicine and Biology, West Dover, United States, July 2016

(xviii) Improving biophysical measurements using quantum mechanics, L. Madsen, W. Muhammad, N. Mauranyapin, M. A. Taylor and W. P. Bowen, invited talk, Quantum and Beyond, Sweden, June 2016.

- (xix) Observation of gravitational waves, Tamara Davis and Warwick Bowen, University of Queensland Colloquium, March 2016
- (xx) Observing gravitational waves: Kilometre-scale laser interferometer with quantum precision, Tamara Davis and Warwick Bowen, presentation for the University of Queensland's top second year science students, August 2016
- (xxi) Evanescent single-molecule biosensing with quantum limited precision, N. P. Mauranyapin, L. S. Madsen, M. A. Taylor, W. P. Bowen, Poster presentation, Gordon Research Conference on Lasers in Medicine and Biology, West Dover, United States, July 2016
- (xxii) Enhanced optical trapping via structured scattering, Muhammad Waleed, Michael A. Taylor, Alexander B. Stilgoe, Halina Rubinsztein-Dunlop and Warwick P. Bowen, IONS KOALA Conference Auckland, New Zealand, Nov 2015
- (xxiii) Quantum noise limited nanoparticle and bio-sensor, Lars S. Madsen, N. Mauranyapin, M. A. Taylor, M. Waleed, W. P. Bowen, SPIE Defence and Commercial Sensing, April 2016
- (xxiv) Quantum noise limited nanoparticle and bio-sensor; and Scanning nearfield imaging of optical nanofibres with sub-nanometre resolution Lars S. Madsen, Christopher Baker, Halina Rubinsztein-Dunlop, N. Mauranyapin, M. A. Taylor, M. Waleed, W. P. Bowen, Air Force Research Laboratory 711th Human Performance Wing, April 2016.
- (xxv) Quantum noise limited nanoparticle and bio-sensor; and Scanning nearfield imaging of optical nanofibres with sub-nanometre resolution, Lars S. Madsen, Christopher Baker, Halina Rubinsztein-Dunlop, N. Mauranyapin, M. A. Taylor, M. Waleed, W. P. Bowen, departmental seminar, Denmark Technical University, June 2016.
- (xxvi) Quantum noise limited nanoparticle and bio-sensor; and Scanning nearfield imaging of optical nanofibres with sub-nanometre resolution, Lars S. Madsen, Christopher Baker, Halina Rubinsztein-Dunlop, N. Mauranyapin, M. A. Taylor, M. Waleed, W. P. Bowen, departmental seminar, the Niels Bohr institute, The University of Copenhagen, June 2016.
- (xxvii) Quantum Enhanced Microscopy, C. Casacio, talk at the Australian Centre of Excellence for Engineered Quantum Systems Idea Factory Workshop, North Stradbroke Island, Australia, May 2016.
- (xxviii) Quantum enhanced microscopy, C. Casacio, L. Madsen, W. P. Bowen, poster at the Gordon Research Conference on Lasers in Medicine and Biology, West Dover, United States, July 2016.

d) manuscripts submitted but not yet published, and

N/A

e) provide a list any interactions with industry or with Air Force Research Laboratory scientists or significant collaborations that resulted from this work.

The project has been undertaken in collaboration with Dr. Hope Beier's laboratory in the Air Force Research Laboratory (AFRL) 711th Human Performance Wing, including several scientific exchanges and a patent application that is in progress. Dr. Beier and her postdoc Dr. Joel Bixler provide expertise and capabilities in nonlinear microscopy, nanoscopy, optogenetics and the effects of radiation on cellular processes, allowing us to guide applications towards those of most relevance to the Air Force and to ensure transfer of technology developed in the project to the AFRL.

During the project we had a range of interactions with industry and researchers in the Air Force Research Laboratory. As part of this AFOSR/AOARD project, PI Bowen and the project postdoc, Dr. Lars Madsen visited Dr. Beiers Laboratory at the Air Force Research Laboratory 711th Human Performance Wing on multiple occasions. One outcome from these visits was a new idea to substantially improve coherent ultrafast microscopy, which allows imaging at billions of frames per second and is used in Dr. Beiers laboratory to study the effect of short pulses of radiation on biological specimens. We are now beginning a new collaboration on this idea.

Within Australia, our AFOSR/AOARD efforts provided part of the platform for PI Bowen to establish, with colleague at the Australian National University and the University of Adelaide, a new entity, Precision Sensing Australia, to engage Australian Defence in next-generation sensing solutions. As part of this effort, PI Bowen was an organizer of the Precision Sensing Workshop in Canberra October 2016, which brought together Australia's leading researchers in this area, as well as high level representatives from Australian Defence, the Commonwealth Scientific and Industrial Research Organisation (CSIRO), the Defence Science and Technology Group, the National Measurement Institute, and the UK Defence Science and Technology Laboratory. In concert, PI Bowen has established the University of Queensland Precision Sensing Initiative, which brings together 17 PIs with a focus on real-world outcomes from state-of-the-art sensing research at the University of Queensland, including the sensors developing in this project, and engagement with the biomedical, aerospace, resources and defense industries. PI Bowen is the Director of this initiative.

PI Bowen was one of only two university researchers invited to speak at the Lockheed Martin Advancing Australian Innovation Symposium for Australian industry, government and technologists in December 2016. He was also invited to speak at the Enabling Technologies Technical Exchange Meeting hosted by the AFOSR and the Australian National Fabrication Facility in May 2016.

Catxere Casacio, one of the project PhD students, has participated in several women in science events. Most particularly, she was invited to participate in the Australian National Press Club event, Future of Women in Science in March 2016. The speakers at the event were Emma Johnston, Director of the Sydney Harbour Research Program at the Sydney Institute of Marine Science; Nalini Joshi, a member of the Commonwealth Science Council and an Australian Research Council Georgina Sweet Australian Laureate Fellow; and Tanya Monro, Deputy Vice Chancellor Research and Innovation at the University of South Australia and an Australian Research Council Georgina Sweet Laureate Fellow.